[0040] Figure 3 illustrates a preferred group of nucleotide fragments for use in A-form portions at the 3' terminus of oligonucleotides of the invention.

[0041] Figure 4 is a plot of the percentage of full length oligonucleotide remaining intact in plasma one hour following administration of an *i.v.* bolus of 5 mg/kg oligonucleotide.

[0042] Figure 5 is a plot of the percentage of full length oligonucleotide remaining intact in tissue 24 hours following administration of an *i.v.* bolus of 5 mg/kg oligonucleotide.

[0043] Figure 6 shows CGE traces of test oligonucleotides and a standard phosphorothioate oligonucleotide in both mouse liver samples and mouse kidney samples after 24 hours.

[0044] Figure 7 shows a graph of the effect of the oligonucleotides of the present invention on *c-raf* expression (compared to control) in bEND cells.

[0045] Figures 8 and 9 shows bar graphs as percent control normalized for the G3PDH signal eighteen hours after treatment with specified compounds.

DESCRIPTION OF PREFERRED EMBODIMENTS

[0046] In one aspect, the present invention is directed to novel oligonucleotides that have certain desirable properties that contribute to increases in binding affinity and/or nuclease resistance, coupled with the ability to serve as substrates for RNase H.

[0047] The oligonucleotide of the invention are formed from a plurality of nucleotides that are joined together via internucleotide linkages. While joined together as a unit in the oligonucleotide, the individual nucleotides of oligonucleotides are of several types. Each of these types contribute unique properties to the oligonucleotide. A first type of nucleotides are joined

together in a continuous sequence that forms a first portion of the oligonucleotide. The remaining nucleotides are of at least one further type and are located in one or more remaining portions or locations within the oligonucleotide. Thus, the oligonucleotides of the invention include a nucleotide portion that contributes one set of attributes and a further portion (or portions) that contributes another set of attributes.

[0048] One attribute that is desirable is eliciting RNase H activity. To elicit RNase H activity, a portion of the oligonucleotides of the invention is selected to have B-form like conformational geometry. The nucleotides for this B-form portion are selected to specifically include ribo-pentofuranosyl and arabino-pentofuranosyl nucleotides. 2'-Deoxy-*erythro*-pentfuranosyl nucleotides also have B-form geometry and elicit RNase H activity. While not specifically excluded, if 2'-deoxy-*erythro*-pentfuranosyl nucleotides are included in the B-form portion of an oligonucleotide of the invention, such 2'-deoxy-*erythro*-pentfuranosyl nucleotides preferably does not constitute the totality of the nucleotides of that B-form portion of the oligonucleotide, but should be used in conjunction with ribonucleotides or an arabino nucleotides. As used herein, B-form geometry is inclusive of both C2'-endo and O4'-endo pucker, and the ribo and arabino nucleotides selected for inclusion in the oligonucleotide B-form portion are selected to be those nucleotides having C2'-endo conformation or those nucleotides having O4'-endo conformation. This is consistent with Berger, *et. al.*, *Nucleic Acids Research*, **1998**, *26*, 2473-2480, who pointed out that in considering the furanose conformations in which nucleosides and nucleotides reside, B-form consideration should also be given to a O4'-endo pucker contribution.

[0049] A-form nucleotides are nucleotides that exhibit C3'-endo pucker, also known as north,

or northern, pucker. In addition to the B-form nucleotides noted above, the A-form nucleotides can be C3'-endo pucker nucleotides or can be nucleotides that are located at the 3' terminus, at the 5' terminus, or at both the 3' and the 5' terminus of the oligonucleotide. Alternatively, A-form nucleotides can exist both in a C3'-endo pucker and be located at the ends, or termini, of the oligonucleotide. In selecting nucleotides that have C3'-endo pucker or in selecting nucleotides to reside at the 3' or 5' ends of the oligonucleotide, consideration is given to binding affinity and nuclease resistance properties that such nucleotides need to impart to the resulting the oligonucleotide.

[0050] Nucleotides selected to reside at the 3' or 5' termini of oligonucleotides of the invention are selected to impart nuclease resistance to the oligonucleotide. This nuclease resistance can also be achieved via several mechanisms, including modifications of the sugar portions of the nucleotide units of the oligonucleotides, modification of the internucleotide linkages or both modification of the sugar and the internucleotide linkage.

[0051] A particularly useful group of nucleotides for use in increasing nuclease resistance at the termini of oligonucleotides are those having 2'-O-alkylamino groups thereon. The amino groups of such nucleotides can be groups that are protonated at physiological pH. These include amines, monoalkyl substituted amines, dialkyl substituted amines and heterocyclic amines such as imidazole. Particularly useful are the lower alkyl amines including 2'-O-ethylamine and 2'-O-propylamine. Such O-alkylamines can also be included on the 3' position of the 3' terminus nucleotide. Thus the 3' terminus nucleotide could include both a 2' and a 3'-O-alkylamino substituent.